REMARKS/ARGUMENTS

Claims 30, 71, 75-76, 85-89, 93, 95-96 and 98-115 will be pending in the present application after entry of this amendment.

Claims 30, 71, 85, 86 and 104-110 have been amended. Claims 71, 86, 106, 108 and 110 were amended to improve their form. Support the amendments to claims 30, 85, 104-105, 107 and 109 can be found throughout the specification, particularly at page 15, lines 18-20; page 16, lines10-13 and 24-26; and page 21, line 23, through page 22, line 3.

Claims 116-122 have been added. Support for claims 116 and 120-122 can be found, e.g., on page 28, lines 10-12. Support for claims 117-119 can be found throughout the specification (*see, e.g.*, page 51, lines 2-3, 8-12 and 19-20; and page 57, line 7).

Applicants thank Examiner Canella and Examiner Nickol for the helpful comments provided during an interview conducted on July 18, 2005. During the interview Applicants provided certain technological background and discussed the novelty of the claimed methods and compositions in view of the cited references and the state of the art at the time that the patent application was filed.

35 U.S.C. § 103

Applicants note with appreciation that claim 89 was found to be patentable over the art.

Claims 30, 71, 75-76, 85-87, 93, 95-96, 98, 101, 103-110 and 113-115 are rejected under 35 U.S.C. § 103 as allegedly obvious in view of the combination of ten references, which will be referred herein as: *Kedar*, *Crowley*, *Steinman*, *Sallusto*, *De La Salle*, *Schwartz*, *Vrba*, *Paul*, *Jurnicic-Winkler*, and *Simitsek*. The Examiner summarizes the teachings of each of the cited references and concludes that at the time of the invention, it would have been obvious "to stimulate an immune response against more than one epitope of a tumor-associated antigen by administering to a patient having a tumor a soluble complex of a tumor-associated antigen complexed to an antibody or antigen binding fragment thereof comprising an Fc region" (Office Action, p. 4). The Examiner states that one would be motivated "to do so", by the teachings of:

- *Kedar* on the desirability of having several T-cell clones directed against different antigenic epitopes of the tumor;
- *Crowley* on the ability of dendritic cells exposed *in vivo* to exogenous antigen to present multiple immunogenic epitopes to T-cells;

- *Steinman* on the capability of dendritic cells to processing complex tumor antigens to peptides to be presented by self MHC products;
- *Sallusto* on the enhancement of soluble antigen presentation by dendritic cells through the uptake of antigen-antibody complexes;
- *De La Salle* on the enhancement of soluble antigen presentation by Langerhan's cells by antigen-antibody complexes and the required processing of the antigen within the antigen-antibody complex after uptake via the Fc receptor of the dendritic cell; and
- *Schwartz* on soluble tumor antigens present in the serum of cancer patients.

The Examiner does not specifically state how the references would be combined, or whether all ten references would need to be combined to reach the claimed invention.

Applicants respectfully traverse this rejection. A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. §103(a); *see Graham v. John Deere Co.*, 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The obviousness determination must be carried out from the perspective of a person having ordinary skill in the art *at the time the invention was made*, guided only by the prior art references and the then-accepted wisdom in the field. *See, e.g., In re Dembiczak*, 50 USPQ 1614 (Fed. Cir. 1999). To guard against the use of hindsight, courts require a rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. *See id.*

Applicants submit that by failing to clearly explain the motivation to combine the prior art references the Examiner has failed to establish a *prima facie* case of obviousness. Further, Applicants submit that in fact a person of ordinary skill in the art would not have been motivated to combine the prior art references cited by the Examiner to reach the claimed invention.

The ten references cited by the Examiner can be divided into two groups: one relating to tumor antigens (tumor immunology) and another one relating to foreign antigens. *See* Declaration of Birgit Schultes, Ph.D., filed under 37 C.F.R. 1.132, Exhibit A (hereinafter "Declaration"), ¶ 4. The issues relating to the elicitation of an immune response against tumor antigens, which are typically self-antigens, are inherently different from the issues relating to elicitation of an immune response against foreign antigens. For example, unlike foreign antigens, tumor antigens are not generally recognized by the immune system. This may be due to the fact that the host usually develops tolerance against tumor antigens and/or the tumor cells develop ways to evade the immune system or elicitation of an immune response. Accordingly, recognizing and eliciting an immune response against foreign antigens is generally a much simpler process than recognizing and eliciting an immune response against tumor antigens. *See* Declaration, ¶¶ 4-8.

Kedar, *Schwartz*, *Steinman*, *Jurnicic-Winkler*, *Vrba* and *Paul* relate to tumor antigens. *Crowley*, *Sallusto*, *De La Salle*, and *Simitsek* relate to foreign antigens. As stated by Dr. Schultes, in view of the fact that foreign antigens and tumor antigens are processed and/or presented differently and do not necessarily elicit the same type of immune responses through the same mechanisms, there would have been no motivation to combine the teachings of references related to the recognition of tumor antigens with the teachings of references related to the recognition of foreign antigens. *See* Declaration, ¶¶ 8, 11 and 12.

Applicants respectfully submit that at the time the invention was made, there was no teaching in the art regarding the use of an antibody/antigen complex to break the immune tolerance that is generally associated with tumor antigens. The only two cited references which may suggest the use of antibody/antigen complexes, *Sallusto* and *De La Salle*, relate to the presentation of ***foreign antigens***, not tumor antigens. *See* Declaration, ¶ 9. Accordingly, neither *Sallusto* nor *De La Salle* teach or suggest the invention of the pending claims which relate to the use of immune complexes involving a tumor antigen which is also a self-antigen.

The Examiner states that the teachings of *Kedar* would motive one of skill in the art "to provide more than one immunogenic epitope of a tumor associated antigen in order to activate more than one T-cell against said antigen." (Office Action, p. 5) Applicants respectfully traverse. *Kedar* only relates to the use of antibodies or T cell clone cocktails to treat cancer. *Kedar* does not disclose or suggest actively eliciting a multi-epitopic immune response against a tumor antigen by administering a tumor antigen/antibody complex, as required by the pending claims. Further, as discussed, at the time the invention was made there was no motivation to combine the teachings of *Kedar* (which relates to tumor antigens) with the teachings of *Crowley*, *Sallusto* or *De La Salle* (which relate to foreign antigens). Notably, the Examiner has not pointed to any such motivation. There is simply nothing that would have motivated one of ordinary skill in the art to combine the teachings of *Kedar* with the teachings of *Crowley, Sallusto* or *De La Salle.*

The Examiner states that it would have been obvious "that the presence of the antibody on the antigen can provide a means for activating T-cells to subdominant epitopes or cryptic epitopes to which tolerance has never been established" (Office Action, p. 5). Although the Examiner does not cite a reference, it appears that this argument is based on the teachings of *Simitsek*. *Simitsek* teaches that antibodies can modulate the presentation of various T cell determinants in a ***foreign antigen in vitro***. *Simitsek* does not disclose that the administration of an antibody/antigen complex to a host could be used to break the immune tolerance generally associated with tumor antigens. Accordingly, *Simitsek* does not disclose or suggest the claimed invention. Further, for the reasons discussed above, there would have been no motivation to combine the teachings of *Simitsek*, which relate to foreign antigens, with the teachings of references relating to tumor antigens.

Finally, the Examiner states that "[o]ne of skill in the art would be motivated to provoke an immune response using a determinant to which tolerance has never been established by the teaching of *Paul* indicating that tolerance is a means by which tumor cells evade immune detection." (Office Action, p. 5) Even if *Paul* indicates that immune tolerance is a means by which tumor cells evade immune detection, *Paul* does not disclose or suggest how to break the immune tolerance to tumor antigens. In particular, *Paul* does not disclose or suggest the claimed methods and compositions which use antibody/antigen complexes to break the immune tolerance associated with tumor antigens.

Moreover, at the time the invention was made, a person of skill in the art would have been discouraged from using immune complexes formed from a soluble tumor antigen and an antibody (or antigen binding fragment thereof) to break the immune tolerance that is generally associated with tumor antigens because the art taught that the presence of circulating immune complexes in the serum of cancer patients was generally correlated with a negative prognosis. *See* Declaration, ¶ 12. Thus, the art taught away from using antigen/antibody complexes to elicit an effective immune response against tumor antigens.

Further, even assuming *arguendo* that a person of ordinary skill in the art would have been motivated to combine the teachings of these two sets of references, a person of ordinary skill in the art would not have had any reasonable expectation that the use of an antigen/antibody complex would break the immune tolerance that is generally associated with the recognition of tumor antigens. In view of the various mechanisms by which hosts can prevent or down-regulate immune responses against tumor antigens, a person of skill in the art could not have reasonably expected that the use of an antigen/antibody complex would break the immune tolerance that is generally associated with tumor antigens. *See* Declaration, ¶ 13.

Applicants respectfully submit that the Examiner is impermissibly using hindsight to find the invention obvious over the prior art. The outstanding Office Action still fails to provide a clear basis for the combination of each of these ten references to reach the claimed invention. The Office Action summarizes the teachings of each reference but fails to put the ten references together and to provide the rationale for doing so. Thus, the Applicants request that the Examiner reconsider and withdraw this rejection. If the Examiner does not withdraw this rejection, Applicants respectfully request that the factual basis for the specific ***combination*** of references be clearly articulated by the Examiner.

Claims 30, 71, 75-76, 85-87, 93, 95-96, 98, 101, 103-110 and 113-115 are rejected as obvious in view of the ten references cited above, and in further view of *Schlom*. The Examiner specifically points to claims 71 and 86 which recite a single chain antibody, a humanized antibody

and a chimeric antibody. According to the Examiner, *Schlom* would render obvious the use of humanized or chimeric antibodies in a soluble complex.

Applicants traverse. As discussed above, the combination of references discussed above does not disclose or suggest the use of antibody/antigen complexes to break the immune tolerance generally associated with tumor antigens. The disclosure of *Schlom* does not cure this deficiency. Accordingly, the claims are not obvious in further view of *Schlom*.

Claims 30, 71, 75-76, 85-87, 93, 95-96, 98, 99, 101, 103-110 and 113-115 are also rejected as obvious in view of the ten references cited above, and in further view of *Dong*. The Examiner specifically points to claim 99 which requires the administration of the antibody or antigen binding fragment thereof with an adjuvant. According to the Examiner, *Dong* teaches the use of cytokines as vaccine adjuvants, and would render obvious the claimed invention.

Applicants traverse. As discussed above, the combination of references discussed above does not disclose or suggest the use of antibody/antigen complexes to break the immune tolerance generally associated with tumor antigens. The disclosure of *Dong* does not cure this deficiency. Accordingly, the claims are not obvious in further view of *Dong*.

Claims 30, 71, 75-76, 85-88, 93, 95-96, 98, 99, 101-110 and 113-115 are also rejected as obvious in view of the ten references cited above, and in further view of *O'Brien* and *Baum*. The Examiner points to claim 88 which recites the use of B43.13 antibody, and to claim 102 which recites CA125 as the tumor associated antigen.

Applicants traverse. As discussed above, the combination of references discussed above does not disclose or suggest the use of antibody/antigen complexes to break the immune tolerance generally associated with tumor antigens. Neither *O'Brien* nor *Baum* cures this deficiency. Accordingly, the claims are not obvious in further view of *O'Brien* and *Baum*.

Claims 30, 71, 75-76, 85-88, 93, 95-96, 98, 99, 101-110 and 113-115 are also rejected as obvious in view of the ten references cited above. The Examiner points to claims 100, 111 and 112 which recite specific dosages of the antibody or antigen fragment to be used in the claimed methods. The Examiner acknowledges that none of the prior art references teach or suggest the specific dosages, but that "it is recognized in the art that the establishment of optimal dosages is empirical but within the purview of one skill in the art."

Applicants traverse. As discussed above, the combination of references discussed above does not disclose or suggest the use of antibody/antigen complexes to break the immune tolerance generally associated with tumor antigens. Accordingly, Applicants respectfully submit that the claims are not obvious in view of the cited references.

In view of the above arguments and the concurrently filed Declaration, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000.

Applicants believe no fee, other than the fee associated with the accompanying petition for a three month extension of time, is due with this response. However, if an additional fee is due, please charge our Deposit Account No. 18-1945, from which the undersigned is authorized to draw, under Order No. AREX-P02-004.

Dated: August 9, 2005

Respectfully submitted,

By _____

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